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ORIGINAL REPORT

Tamoxifen and Risk of Contralateral Breast Cancer for *BRCA1* and *BRCA2* Mutation Carriers

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ABSTRACT

Purpose
To determine whether adjuvant tamoxifen treatment for breast cancer (BC) is associated with reduced contralateral breast cancer (CBC) risk for *BRCA1* and/or *BRCA2* mutation carriers.

Methods
Analysis of pooled observational cohort data, self-reported at enrollment and at follow-up from the International *BRCA1*, and *BRCA2* Carrier Cohort Study, Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer, and Breast Cancer Family Registry. Eligible women were *BRCA1* and *BRCA2* mutation carriers diagnosed with unilateral BC since 1970 and no other invasive cancer or tamoxifen use before first BC. Hazard ratios (HRs) for CBC associated with tamoxifen use were estimated using Cox regression, adjusting for year and age of diagnosis, country, and bilateral oophorectomy and censoring at contralateral mastectomy, death, or loss to follow-up.

Results
Of 1,583 *BRCA1* and 881 *BRCA2* mutation carriers, 383 (24%) and 454 (52%), respectively, took tamoxifen after first BC diagnosis. There were 520 CBCs over 20,104 person-years of observation. The adjusted HR estimates were 0.38 (95% CI, 0.27 to 0.55) and 0.33 (95% CI, 0.22 to 0.50) for *BRCA1* and *BRCA2* mutation carriers, respectively. After left truncating at recruitment to the cohort, adjusted HR estimates were 0.58 (95% CI, 0.29 to 1.13) and 0.48 (95% CI, 0.22 to 1.05) based on 657 *BRCA1* and 426 *BRCA2* mutation carriers with 100 CBCs over 4,392 person-years of prospective follow-up. HRs did not differ by estrogen receptor status of the first BC (missing for 56% of cases).

Conclusion
This study provides evidence that tamoxifen use is associated with a reduction in CBC risk for *BRCA1* and *BRCA2* mutation carriers. Further follow-up of these cohorts will provide increased statistical power for future prospective analyses.

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INTRODUCTION

Women who carry a mutation in *BRCA1* or *BRCA2* have a high lifetime risk of breast cancer (BC).[1] Bilateral mastectomy and premenopausal bilateral salpingo-oophorectomy (BSO) are associated with a reduced BC risk of greater than 90%[2,3] and approximately 50%, respectively,[4] but are not acceptable interventions for many women.[5,6] Randomized, placebo-controlled primary prevention trials of women who are at increased risk of BC have shown that selective estrogen receptor modulators (SERMs), such as tamoxifen, reduce BC risk by 40%.[7-11] The preventive effect of tamoxifen is sustained for at least 5 years after cessation of therapy,[11] and the absolute risk of serious adverse effects is low, particularly for premenopausal women.[9,12] For women in the general population, randomized controlled trials have also shown that adjuvant tamoxifen treatment after a first BC diagnosis halves the risk of contralateral breast cancer (CBC).[13] However, it is uncertain whether tamoxifen has any efficacy for women carrying mutations in *BRCA1* or *BRCA2*, and it is not commonly prescribed to carriers[14,15] for the purpose of BC prevention.

Inadequate data regarding efficacy is a major barrier to prescribing SERMS to *BRCA1* and *BRCA2* mutation carriers to prevent BC.[16] Randomized primary prevention trials of mutation carriers are unlikely to be feasible and would take many years to generate reliable conclusions. Prospective observational studies of the efficacy of SERMS for primary prevention of BC would depend on uptake of tamoxifen by mutation carriers and would also take many years. Yet the issue is an important one right now for the tens of thousands of women who currently know that they carry a *BRCA1* or *BRCA2* mutation. Information about the efficacy or otherwise of tamoxifen for the prevention of CBC could assist *BRCA1* and *BRCA2* mutation carriers make decisions about whether to take tamoxifen for primary BC prevention. It might also have implications for the adjuvant treatment of *BRCA1* and *BRCA2* mutation carriers who do not wish to have bilateral mastectomy after an initial diagnosis of a hormone receptor–negative BC.

The aim of this study was to determine whether adjuvant tamoxifen treatment for first BC is associated with a reduction in the risk of CBC for *BRCA1* and/or *BRCA2* mutation carriers and whether the strength of any association differs according to the estrogen receptor (ER) status of the first BC.

METHODS

Participants

Participants were female *BRCA1* or *BRCA2* mutation carriers from Europe, Australia, New Zealand, the United States, and Canada, enrolled between September 1, 1993, and December 2, 2009, in three cohort studies; the International *BRCA1* and *BRCA2* Carrier Cohort Study (IBCCS),[17] the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab),[18] and the Breast Cancer Family Registry (BCFR).[19] All cohorts include participants recruited through BC family clinics, and the BCFR also includes some population-based recruitment. All participants provided written informed consent, and all studies were approved by the relevant institutional review boards.

A woman was eligible for the current study if she had a pathogenic mutation in *BRCA1* or *BRCA2* and a BC diagnosed since 1970 (when tamoxifen started to be prescribed for early-stage BC) that was not bilateral at the time of diagnosis (defined as within 6 months of first BC diagnosis). Women with a history of other invasive cancers or tamoxifen use before their first BC were excluded.

Data Collection

Information on family cancer history, demographics, potential risk factors for BC (eg, exogenous hormone use, alcohol intake, and reproductive history), uptake of surgical and medical prevention strategies, and cancer treatment including use of tamoxifen and chemotherapy was self-reported at cohort entry and at follow-up. Cancer outcomes were self-reported and/or collected by linkage with a cancer registry. Each study in each cohort collected this information systematically using similar questionnaires. Frequency of follow-up varied between studies. Pathology data were abstracted from several sources, including diagnostic pathology reports, medical records, and cancer registry records, or through central pathology review.

Statistical Analysis

Participants were considered to have used tamoxifen if they took it for any period of time after their first BC diagnosis. Hazard ratios (HRs) for CBC associated with tamoxifen use (no, yes) after first BC, excluding use after CBC, were estimated separately for *BRCA1* and *BRCA2* mutation carriers using Cox regression, modeling time from first BC diagnosis to the development of CBC. Analysis time was censored at the date of contralateral mastectomy, death, or last follow-up.

Two main analyses were performed. The first combined retrospective (ie, time before cohort entry) and prospective (ie, time after cohort entry) follow-up. For this analysis, all women were eligible, and follow-up started at date of diagnosis of the first BC. To investigate whether the inclusion of prevalent CBC cases may have introduced bias, a second analysis was performed that applied left truncation of analysis time at the date of cohort entry and therefore considered outcome data from prospective follow-up only. Age and year of diagnosis (both continuous), country of residence (categorical), and BSO (dichotomous, time-varying) were considered as covariates in all multivariable analyses and were included in analyses of retrospective follow-up data. Adjustment for year of diagnosis and BSO made no substantial difference to HR estimates from the analyses of prospective data only; given the smaller number of contralateral events, only age at diagnosis and country of residence were included in the final prospective models. Robust estimates of variance were derived to account for the nonindependence of women from the same family. ER status of the first BC was considered as a covariate and as a stratifying variable in separate multivariable analyses of the combined retrospective and prospective data. Sensitivity analyses were undertaken using the combined and prospective-only data.

These included stratifying by menopausal status at diagnosis of the first BC, adjusting for chemotherapy use (no, yes) and histologic subtype (lobular, nonlobular), adjusting for use of oral contraceptives (no, yes) or hormone replacement therapy after the first BC diagnosis (no, yes), excluding those who took other endocrine therapy (eg, aromatase inhibitors or gonadotropin-releasing hormone agonists) after the first BC, and censoring at the date of the first subsequent ipsilateral breast event or at diagnosis of the first nonbreast primary cancer.

All statistical analyses were conducted using STATA 10 (STATA, College Station, TX). Gene-specific post hoc power calculations were carried out using StatCalc in Epi Info[20] based on the number of participants the observed prevalence of tamoxifen use, and the observed 11% of nonusers who developed contralateral disease during follow-up.

RESULTS

A total of 3,267 *BRCA1* and *BRCA2* mutation carriers with a personal history of BC were identified from the three cohorts. Of these, 803 were excluded because of first BC diagnosis before 1970 (n = 107), CBC occurring within 6 months after the first BC diagnosis (n = 115), no follow-up after the first BC diagnosis (n = 130), other invasive cancer before first BC diagnosis (n = 86), use of tamoxifen before their first BC diagnosis (n = 34), and missing information on tamoxifen use or information only available from a relative (proxy; n = 331). Thus the final sample of 2,464 women comprised 1,583 *BRCA1* and 881 *BRCA2* mutation carriers, 95.7% of whom were ascertained through BC family clinics and an estimated 96% of whom were of white European origin. Prospective follow-up data (since date of cohort entry) were available for 1,083 women (44%), comprising 657 *BRCA1* and 426 *BRCA2* mutation carriers who had been diagnosed with their first BC a median of 3.9 years before study entry.

Participant characteristics are shown in Table 1. The median time since diagnosis of first BC was 6.6 years, and the median time since cohort entry was 3.2 years. ER status of the first BC was known for 44% of women. Where ER status was known, the first BC was ER negative for 76% of *BRCA1* mutation carriers and ER positive for 77% of *BRCA2* mutation carriers. In total, 24% of *BRCA1* and 52% of *BRCA2* mutation carriers used tamoxifen after their first BC. Overall, 67% of those with an ER-positive first BC used tamoxifen (60% and 71% for *BRCA1* and *BRCA2* mutation carriers, respectively) compared with 17% of those with an ER-negative first BC (15% and 25%, respectively). A total of 581 *BRCA1* mutation carriers (37%) and 289 *BRCA2*

Table 1. Participant Characteristics

Characteristic	*BRCA1* Mutation Carriers (n = 1,583) No.	%	*BRCA2* Mutation Carriers (n = 881) No.	%
Data available				
Retrospective only	926	58	455	52
Prospective	657	42	426	48
Follow-up in years				
Since first BC diagnosis				
Median	6.5		6.6	
Interquartile range	3.0-11.8		3.0-11.2	
Since cohort enrollment				
Median	3.4		3.1	
Interquartile range	2.0-6.1		1.6-6.0	
Cohort				
IBCCS	1,063	67	509	58
kConFab	321	20	242	27
BCFR	199	13	130	15
Country of residence				
Australia	286	18	226	26
Austria	65	4	18	2
Canada	47	3	44	5
France	267	17	143	16
Italy	21	1	10	1
New Zealand	21	1	8	1
Poland	50	3	0	
Spain	41	3	48	5
The Netherlands	202	13	31	4
United States of America	181	11	117	13
United Kingdom	297	19	204	23
Other*	105	7	32	4
Year of first BC diagnosis				
1970-1979	97	6	35	4
1980-1989	341	22	157	18
1990-1999	815	51	442	50
≥ 2000	330	21	247	28
Age at first BC diagnosis, years				
<40	801	51	311	35
40-49	527	33	355	40
50-59	200	13	159	18
≥ 60	55	3	56	6
Menopausal status at first BC diagnosis				
Pre/perimenopausal	1,349	85	691	78
Postmenopausal	234	15	190	22
Estrogen receptor status of first BC				
Negative	504	32	100	11
Positive	157	10	331	38
Unknown	922	58	450	51
Took tamoxifen for first BC				
No	1,200	76	427	48
Yes	383	24	454	52
Yes, ER-negative first BC	76	15	25	25
Yes, ER-positive first BC	94	60	234	71
Chemotherapy administered for first BC				
No	233	15	148	17
Yes	717	45	366	42
Unknown	633	40	367	42
Bilateral oophorectomy				
No	1,002	63	592	67
Yes	581	37	289	33

Abbreviations: BC, breast cancer; BCFR, Breast Cancer Family Registry; ER, estrogen receptor; IBCCS, International *BRCA1*, and *BRCA2* Carrier Cohort Study; kConFab, Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer.

*European countries, with the exception of eight *BRCA1* mutation carriers and one *BRCA2* mutation carrier from other countries.

mutation carriers (33%) underwent BSO, either before (n = 64 and 44, respectively) or after (n = 517 and 245, respectively) their first BC.

Several tumor and patient characteristics are associated with risk of CBC,[21,22] although there are only limited data on these associations for *BRCA1* and *BRCA2* mutation carriers.[23-25] Table 2 compares tamoxifen users and nonusers with regard to such characteristics. Tamoxifen users tended to be older at first BC diagnosis ($P < .001$), which was more likely to have been ER positive ($P < .001$) and of lobular histology ($P = .01$). Tamoxifen users were also more likely to have received chemotherapy ($P = .001$) and to have had BSO ($P < .001$).

Table 2. Characteristics Potentially Associated With Contralateral BC Risk: Tamoxifen Users Versus Nonusers

Characteristic	Tamoxifen Users No.	%	Tamoxifen Nonusers No.	%	*P**
Mutation type					< .001
BRCA1	383	46	1,200	74	
BRCA2	454	54	427	26	
Age at first BC, years					< .001
Median	43		40		
Interquartile range	37-49		34-47		
Estrogen receptor status of first BC					
Negative	101	24	502	76	
Positive	328	76	160	24	< .001
Unknown	408		965		
Histology of first BC					
Lobular	19	3	16	2	
Nonlobular	532	97	1,039	98	.01
Unknown	286		572		
Chemotherapy administered for first BC					
No	105	21	276	29	
Yes	399	79	684	71	.001
Unknown	333		667		
Bilateral oophorectomy					
No	486	58	1,108	68	
Yes	351	42	519	32	< .001

Abbreviation: BC, breast cancer.

*Determined using Fisher's exact test on known values for all characteristics except age, for which the rank-sum test was applied.

Table 3. Association Between Tamoxifen Use After First BC and CBC

Variable	No.	Person-Years	CBC No.	CBC %/Person-Year	HR	95% CI	*P*
BRCA1 mutation carriers							
Combined data							
Took tamoxifen for first BC							
No	1,200	9,893	338	3.4	1.00		
Yes	383	3,086	35	1.1	0.38*	0.27 to 0.55	< .001
Prospective data only							
Took tamoxifen for first BC							
No	481	1,989	54	2.7	1.00		
Yes	176	716	12	1.7	0.58†	0.29 to 1.13	.1
BRCA2 mutation carriers							
Combined data							
Took tamoxifen for first BC							
No	427	3,762	115	3.1	1.00		
Yes	454	3,364	32	1.0	0.33*	0.22 to 0.50	< .001
Prospective data only							
Took tamoxifen for first BC							
No	191	791	21	2.7	1.00		
Yes	235	896	13	1.5	0.48†	0.22 to 1.05	.07

Abbreviations: BC, breast cancer; CBC, contralateral breast cancer; HR, hazard ratio.
*Adjusted for age at diagnosis (continuous), year of diagnosis (continuous), bilateral prophylactic oophorectomy (time varying), and country of residence (categorical, as per Table 1).
†Adjusted for age at diagnosis (continuous) and country (categorical: Australia, Canada, France, United States, United Kingdom, other).

CBCs occurred in 520 women (24% of *BRCA1* and 17% of *BRCA2* mutation carriers), and 100 of these occurred after cohort entry. Results from Cox regression analysis assessing an association between tamoxifen use after first BC and risk of CBC are shown in Table 3 and Figure 1. For *BRCA1* mutation carriers, from analysis of the combined retrospective and prospective data, the estimated HR was 0.38 (95% CI, 0.27 to 0.55; $P < .001$). From analysis using only the prospective data, the estimated HR was 0.58 (95% CI, 0.29 to 1.13; $P = .1$). For *BRCA2* mutation carriers, the corresponding HRs were 0.33 (95% CI, 0.22 to 0.50; $P < .001$) and 0.48 (95% CI, 0.22 to 1.05; $P = .07$), respectively. There were no significant differences in the HR estimates between *BRCA1* and *BRCA2* mutation carriers using the combined data ($P_{heterogeneity} = .7$) or the prospective data only ($P_{heterogeneity} = .9$), nor were the results different between *BRCA1* and *BRCA2* mutation carriers based on the retrospective data only ($P_{heterogeneity} = .7$). Analyses of combined data adjusting for, or stratifying on, ER status of the first BC revealed that the observed associations were not accounted for by this tumor characteristic; there was no evidence that the HRs for tamoxifen use differed by ER status ($P_{heterogeneity} = .3$ and .3 for *BRCA1* and *BRCA2* mutation carriers, respectively), although the number of ER-positive BCs in *BRCA1* mutation carriers and ER-negative BCs in *BRCA2* mutation carriers was small (Table 4). The results from all sensitivity analyses were similar (Table 5).

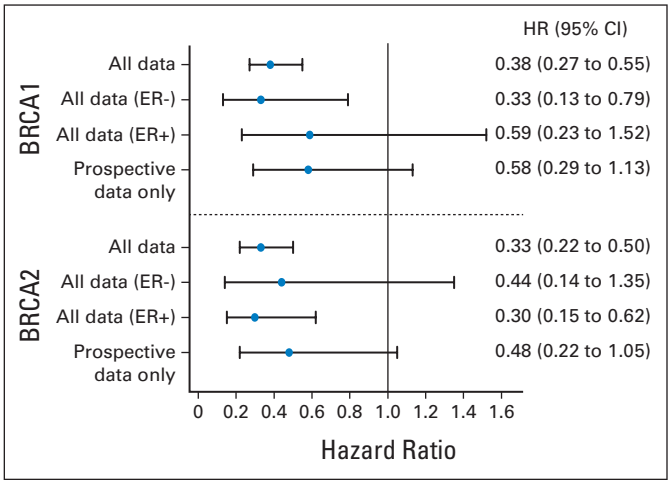

Fig 1. Hazard ratio (HR) estimates (represented by circles) and corresponding 95% CIs (represented by horizontal lines) for risk of contralateral breast cancer associated with tamoxifen use by women with *BRCA1* mutations (BRCA1) and *BRCA2* mutations (BRCA2). Separate estimates are provided based on combined retrospective and prospective data, overall, and by estrogen receptor (ER) status and on prospective data only.

For *BRCA1* mutation carriers who were premenopausal at first BC diagnosis, the association of reduced BC risk with tamoxifen was weaker for those who underwent BSO compared with those who did not (using combined retrospective and prospective data, HR = 0.70 [95% CI, 0.32 to 1.53] *v* 0.26 [95% CI, 0.16 to 0.43]; $P_{heterogeneity} = .004$). This difference was less evident when the analysis was restricted to the prospective data (HR = 0.61 [95% CI, 0.23 to 1.65] *v* 0.40 [95% CI, 0.12 to 1.32]; $P_{heterogeneity} = .3$). For *BRCA2* mutation carriers from the combined data, the corresponding HR estimates were 0.70 (95% CI, 0.27 to 1.82) versus 0.21 (95% CI, 0.12 to 0.36; $P_{heterogeneity} = .08$), and from prospective data only, they were 0.76 (95% CI, 0.10 to 5.64) versus 0.33 (95% CI, 0.06 to 1.91; $P_{heterogeneity} = .5$).

DISCUSSION

In this study, use of tamoxifen after first BC was associated with reduced risk of CBC for *BRCA1* and *BRCA2* mutation carriers based

Table 4. Analysis by ER Status of First Breast Cancer (combined retrospective and prospective data)

Variable	Person-Years		CBC						
			No Tam		Tam				
	No Tam	Tam	No.	%/Person-Year	No.	%/Person-Year	HR	95% CI	*P*
BRCA1 mutation carriers									
ER negative	428	76	2,628	521	95	3.6	6	1.2	0.33†	0.13 to 0.79	.01
ER positive	63	94	482	547	12	2.5	7	1.3	0.59*	0.23 to 1.52	.3
Adjusted for ER status	491	170	3,110	1,068	107	3.4	13	1.2	0.44‡	0.25 to 0.85	.01
BRCA2 mutation carriers									
ER negative	75	25	531	264	14	2.6	3	1.1	0.44*	0.14 to 1.35	.2
ER positive	97	234	558	1,428	22	3.9	14	1.0	0.30†	0.15 to 0.62	.001
Adjusted for ER status	172	259	1,090	1,692	36	3.3	17	1.0	0.33‡	0.17 to 0.64	.001

Abbreviations: CBC, contralateral breast cancer; ER, estrogen receptor; HR, hazard ratio; No Tam, did not take tamoxifen for first breast cancer; Tam, took tamoxifen for first breast cancer.

*Adjusted for age at diagnosis (continuous).

†Adjusted for age at diagnosis (continuous) and country of residence (categorical: Australia, France, the Netherlands, United Kingdom, United States, other).

‡Adjusted for age at diagnosis (continuous), year of diagnosis (continuous), bilateral prophylactic oophorectomy (time varying), and country of residence (categorical, as in †).

on combined retrospective and prospective data. No differences in the reduction of risk associated with tamoxifen use were found by the ER status of the first BC. Our findings are consistent with those of other smaller observational studies that used retrospective data[26-29] and strengthen those findings.

Only one other prospective study has examined the association between tamoxifen use and BC risk for *BRCA1* and *BRCA2* mutation carriers. In the primary prevention setting, a substudy of a double-blind, placebo-controlled trial estimated the HRs for BC with tamoxifen use to be 1.67 (95% CI, 0.32 to 10.7) and 0.38 (95% CI, 0.06 to 1.56) for *BRCA1* and *BRCA2* mutation carriers, respectively[15]; the wide CIs suggest that these analyses were essentially uninformative. In the current study, when the analyses were restricted to prospective data only, there was only weak evidence that tamoxifen use is associated with reduced risk of CBC, with statistically nonsignificant HR estimates that were less than 1. The post hoc power for the analysis of prospective data only was limited; for each of *BRCA1* and *BRCA2* mutation carriers, there was 80% power at $P < .05$ to detect HRs of 0.35 or less. Therefore, our statistically nonsignificant findings from analysis of the prospective data only should not necessarily be interpreted as a lack of confirmation of the highly significant results from the analysis of the pooled retrospective and prospective data, especially given the consistency in the HR estimates from the two analyses.

Previous studies have suggested that tamoxifen use only reduces the risk of ER-positive BC.[7-11] The majority (75% to 80%) of BCs arising in *BRCA2* mutation carriers are ER positive,[30] whereas most BCs arising in *BRCA1* mutation carriers are ER negative at the time of diagnosis.[31] Nevertheless, estrogen might be important in the pathogenesis of BCs in *BRCA1* mutation carriers, particularly given the observation that premenopausal bilateral oophorectomy is associated with reduced BC risk for *BRCA1* mutation carriers[3] and that preclinical data suggest that *BRCA1*-associated BCs may have an estrogen-responsive occult phase.[32-34] A link between estrogen and BC development in *BRCA1* mutation carriers is suggested by the finding that two single-nucleotide polymorphisms located close to *ESR1* (which encodes ER α) are associated with BC risk in *BRCA1* mutation carriers.[35] Furthermore, ER β is commonly expressed in BCs of *BRCA1* mutation carriers[36,37] and could be a target for tamoxifen.[38] Thus there are important plausible mechanisms by which tamoxifen might prevent BC for both *BRCA1* and *BRCA2* mutation carriers.[39]

BRCA1 and *BRCA2* mutation carriers have increased risks of both breast and high-grade serous gynecologic cancers.[1] Given that screening for the latter is ineffective,[40-45] many carriers elect to undergo premenopausal BSO, which dramatically reduces their risk of serous gynecologic cancer and is associated with about a halving of BC risk.[4] Therefore, in the primary prevention setting, an important clinical question is whether tamoxifen use might further reduce BC risk for mutation carriers who have had premenopausal BSO. Although we could not distinguish between pre- and postmenopausal BSO, our findings suggest that the inverse association between tamoxifen use and risk of CBC is stronger if ovaries are still in situ.

The strengths of the current study include the systematic data collection and the inclusion of women with an ER-negative first BC who received tamoxifen. The latter occurred because in many countries in the 1970s and early 1980s, adjuvant tamoxifen was prescribed to postmenopausal women with BC irrespective of hormone receptor status. Another strength of this study is the relatively large sample size, although, despite this, prospective data were limited.

A major limitation of the study is the nonrandomized design, which could have resulted in biased estimates owing to nonrandom use of tamoxifen. Compared with nonusers, tamoxifen users were significantly older and more likely to have had an ER-positive first BC, to have received chemotherapy, and to have had BSO, all features generally associated with reduced risk of CBC. However, adjustment for age at diagnosis and ER status of the first BC in multivariate analysis, as well as stratifying on ER status, made no substantive difference to the results. Sensitivity analyses showed little influence of adjustment for chemotherapy or histologic subtype. Thus it is unlikely that our finding of an association between tamoxifen use and reduced CBC is explained solely by nonrandom use of tamoxifen.

A randomized study to address this secondary prevention question is unlikely to be feasible given that (1) a substantial proportion of young mutation carriers undergo contralateral mastectomy after their first BC diagnosis,[46,47] and (2) it could only be conducted in women with ER-negative BC because adjuvant endocrine therapy (with tamoxifen and/or an aromatase inhibitor) is the standard of care for

Table 5. Association Between Tamoxifen Use and Risk of CBC: Sensitivity Analyses

Variable	No.	CBC	Person-Years	HR	95% CI
BRCA1 mutation carriers					
Combined data*					
Main analysis	1,583	373	12,979	0.38	0.27 to 0.55
Premenopausal women	1,312	329	11,045	0.35	0.24 to 0.53
Postmenopausal women	234	35	1,699	0.51	0.20 to 1.29
Chemotherapy use known	950	194	7,306	0.41	0.26 to 0.67
Adjusted for chemotherapy	950	194	7,306	0.41	0.25 to 0.67
Histology of first BC known	1,047	244	8,076	0.33	0.20 to 0.53
Adjusted for histology	1,047	244	8,076	0.33	0.20 to 0.54
Adjusted for use of OC or HRT	1,583	373	12,979	0.38	0.27 to 0.55
Excluding women who used OC or HRT	1,419	345	11,536	0.35	0.24 to 0.51
Excluding women who used other endocrine therapy	1,574	372	12,940	0.38	0.27 to 0.55
Censoring at ipsilateral events after first BC	1,572	351	12,499	0.38	0.26 to 0.56
Censoring at diagnosis of non-breast primary cancers	1,580	364	12,495	0.35	0.24 to 0.51
Prospective data only†					
Main analysis	657	66	2,705	0.58	0.29 to 1.13
Premenopausal women	550	59	2,295	0.55	0.27 to 1.13
Postmenopausal women	93	5	357	—	
Chemotherapy use known	385	39	1,827	0.61	0.26 to 1.48
Adjusted for chemotherapy	385	39	1,827	0.60	0.25 to 1.47
Histology of first BC known	297	37	1,207	0.43	0.17 to 1.08
Adjusted for histology	297	37	1,207	0.45	0.18 to 1.14
Adjusted for use of OC or HRT	657	66	2,705	0.57	0.29 to 1.12
Excluding women who used OC or HRT	579	60	2,379	0.56	0.28 to 1.11
Excluding women who used other endocrine therapy	649	65	2,688	0.58	0.29 to 1.15
Censoring at ipsilateral events after first BC	629	60	2,588	0.58	0.28 to 1.18
Censoring at diagnosis of non-breast primary cancers	609	62	2,462	0.49	0.23 to 1.01
BRCA2 mutation carriers					
Combined data*					
Main analysis	881	147	7,125	0.33	0.22 to 0.50
Premenopausal women	667	117	5,559	0.28	0.17 to 0.46
Postmenopausal women	190	26	1,382	0.41	0.18 to 0.92
Chemotherapy use known	514	78	4,117	0.39	0.22 to 0.70
Adjusted for chemotherapy	514	78	4,117	0.41	0.23 to 0.75
Histology of first BC known	559	95	4,212	0.43	0.26 to 0.72
Adjusted for histology	559	95	4,212	0.43	0.26 to 0.72
Adjusted for use of OC or HRT	881	147	7,124	0.32	0.22 to 0.49
Excluding women who used OC or HRT	803	136	6377	0.35	0.23 to 0.53
Excluding women who used other endocrine therapy	863	146	7,051	0.33	0.22 to 0.49
Censoring at ipsilateral events after first BC	869	138	6,823	0.37	0.24 to 0.56
Censoring at diagnosis of non-breast primary cancers	880	143	6,943	0.32	0.21 to 0.48
Prospective data only†					
Main analysis	426	34	1,687	0.48	0.22 to 1.05
Premenopausal women	321	23	1,301	0.58	0.21 to 1.61
Postmenopausal women	91	8	348	0.35	0.08 to 1.48
Chemotherapy use known	256	26	1,182	0.43	0.16 to 1.15
Adjusted for chemotherapy	256	26	1,182	0.55	0.21 to 1.45
Histology of first BC known	195	23	692	0.79	0.31 to 2.05
Adjusted for histology	195	23	692	0.78	0.31 to 1.99
Adjusted for use of OC or HRT	426	34	1,687	0.45	0.21 to 0.99
Excluding women who used OC or HRT	386	32	1,512	0.46	0.21 to 1.04
Excluding women who used other endocrine therapy	412	33	1,650	0.47	0.21 to 1.05
Censoring at ipsilateral events after first BC	410	31	1,607	0.48	0.21 to 1.08
Censoring at diagnosis of non-breast primary cancers	412	32	1,586	0.46	0.20 to 1.05

Abbreviations: BC, breast cancer; CBC, contralateral breast cancer; HR, hazard ratio; HRT, hormone replacement therapy; OC, oral contraceptive.
*Analysis adjusted for age at diagnosis (continuous), year of diagnosis (continuous), bilateral prophylactic oophorectomy (time varying), and country of residence (categorical).
†Analysis adjusted for age at diagnosis (continuous) and country (categorical).

ER-positive first BC. Certainly it would take many years to initiate and complete such a trial so that results would not be available for more than a decade.

The large proportion of participants in the current study with missing ER data for the first BC reduced the power of the corresponding stratified analysis. Nevertheless, because ER status is associated with both tamoxifen use and risk of CBC,[22] it is convincing that the stratified analyses gave consistent results.

The analyses of all data combined included prevalent cases of BC and therefore could be subject to survival bias. For this reason, we repeated the analyses using prospective data only. The results were consistent, but the inverse associations were somewhat attenuated.

Tamoxifen has not been widely prescribed for primary prevention of BC for *BRCA1* and *BRCA2* mutation carriers, in part because there has been inadequate evidence of efficacy.[16] The data presented here add to the current evidence base. Some clinicians might consider the statistically significant inverse association between tamoxifen use and development of CBC, seen in the combined analysis, as adequate reason to prescribe tamoxifen for BC prevention in *BRCA1* and *BRCA2* mutation carriers, despite the fact that the association was not confirmed by the less strongly powered prospective analysis. Others might not consider the evidence to be sufficient. Because mutations in *BRCA1* and *BRCA2* are associated with early-onset BC, premenopausal women are the most relevant group in this setting. Tamoxifen can cause hot flushes and night sweats, but for premenopausal women, the main serious adverse effect is deep venous thrombosis; the risk is similar to that from use of the combined oral contraceptive pill.[48,49] Endometrial cancer risk is increased for women who take tamoxifen for treatment of BC or for BC prevention. Some small retrospective observational studies have suggested increased endometrial cancer risk specifically for *BRCA1* and *BRCA2* mutation carriers who take tamoxifen,[50,51] although caution must be exercised in interpreting these findings.[52] Therefore, for *BRCA1* and *BRCA2* mutation carriers with breast tissue, particularly those who have not undergone premenopausal BSO, the option of tamoxifen for BC prevention should perhaps be discussed along with the evidence of benefits and potential adverse effects, allowing women themselves to decide whether they wish to use the medication.

This study provides observational evidence that, for *BRCA1* and *BRCA2* mutation carriers, tamoxifen use for first BC might reduce the risk of CBC. Further follow-up of these cohorts will provide increased statistical power for prospective analyses and thus a more definitive answer to this important question in the future.

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